

Osteoporosis



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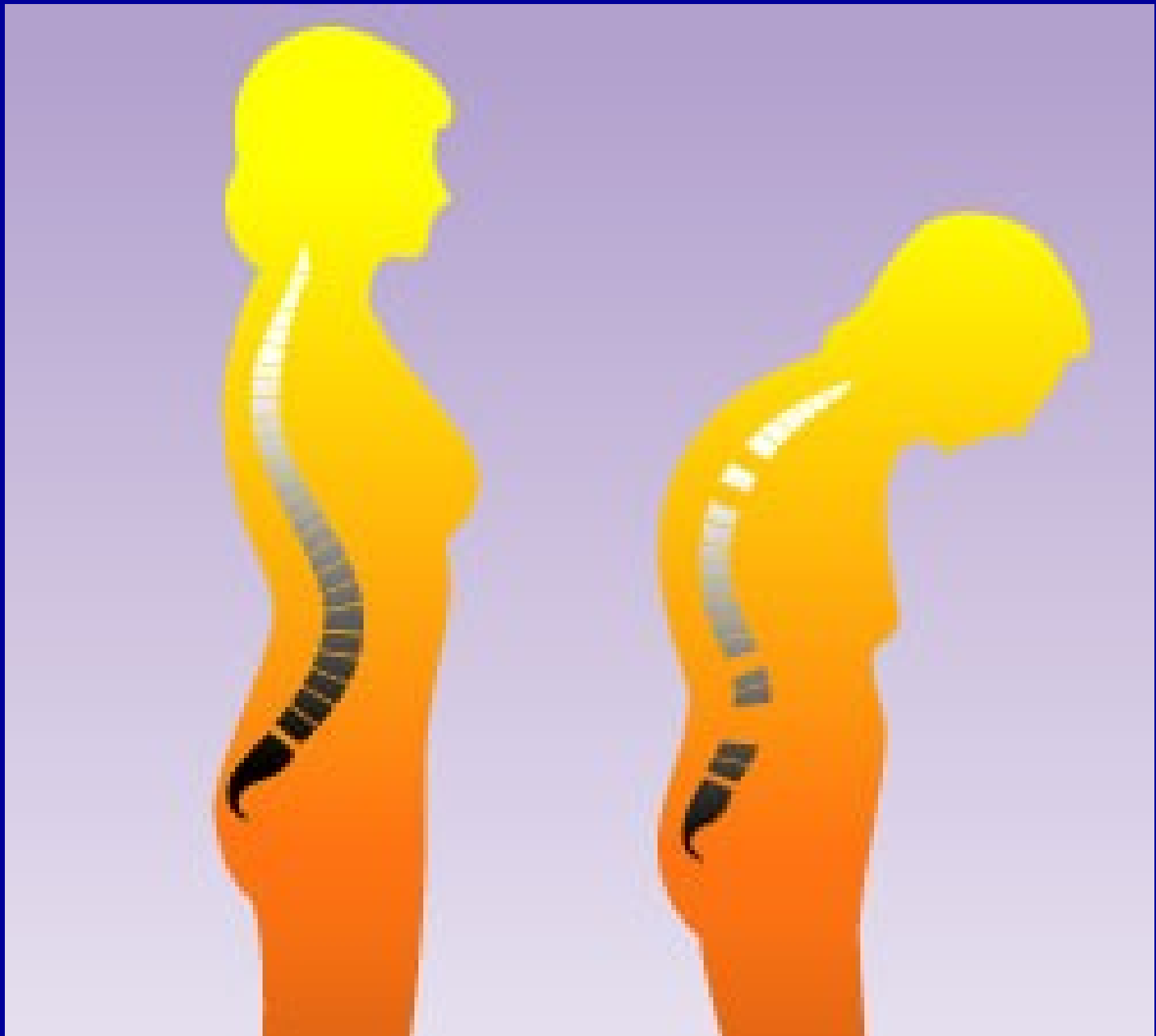
OBJECTIVES

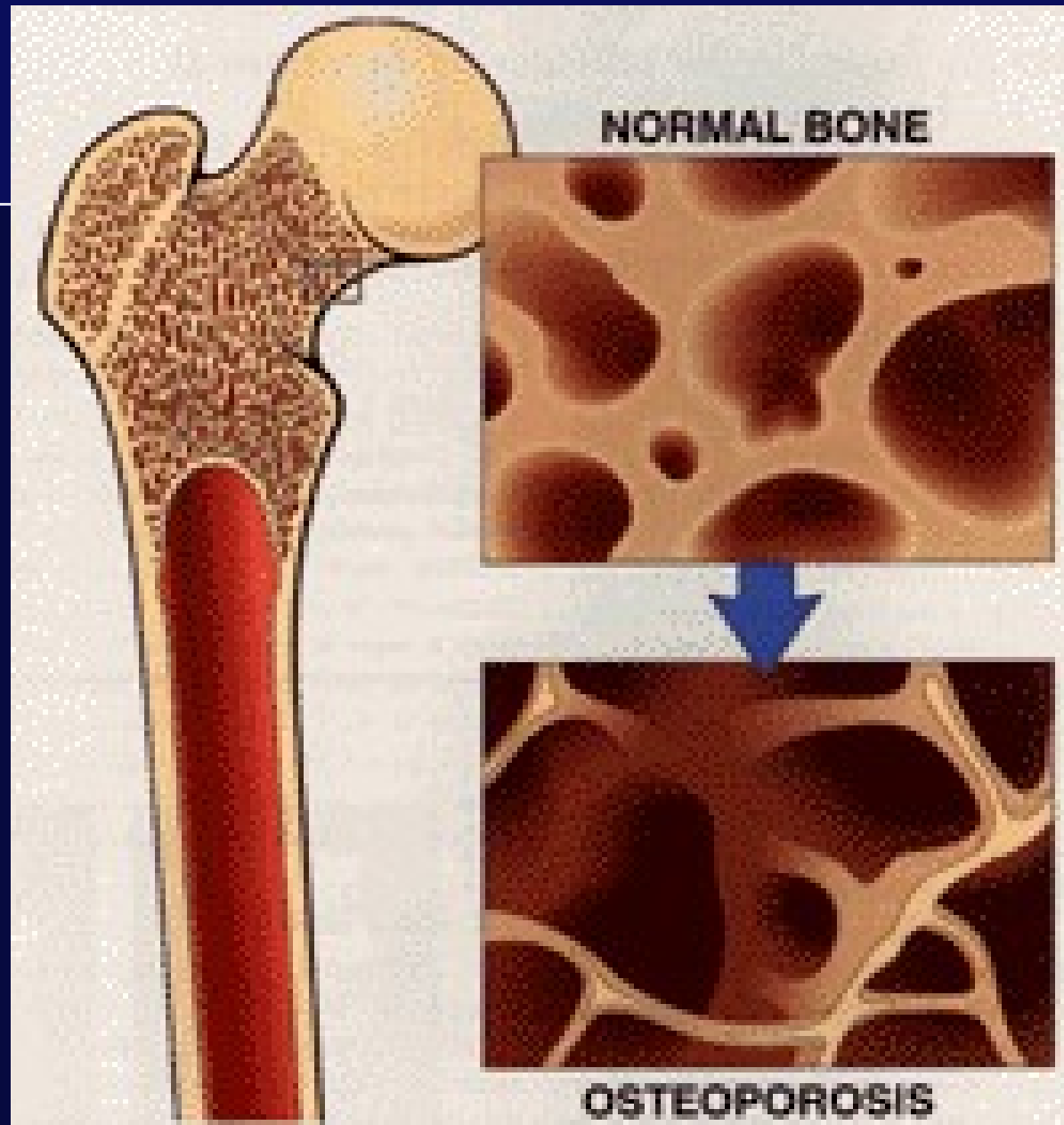
- Know and understand:
 - How to diagnose osteopenia and osteoporosis
 - The pathogenesis of osteoporosis
 - Common secondary causes of bone loss
 - Prevention and treatment strategies for osteoporosis
 - How to diagnose and treat osteomalacia

Osteoporosis

“...is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.”

Consensus Development Conference: Diagnosis, Prophylaxis, and Treatment of Osteoporosis, *Am J Med* 1993;94:646-650. WHO Study Group 1994. 3





BONE REMODELING

- **Bone repairs itself by actively remodeling**
 - **bone resorption (osteoclasts)**
 - **bone formation (osteoblasts)**

- **The remodeling cycle may become unbalanced**
 - **after menopause; with aging in men and women**
 - **bone resorption increases more than bone formation, resulting in net bone loss**

LIFETIME CHANGES IN BONE MASS

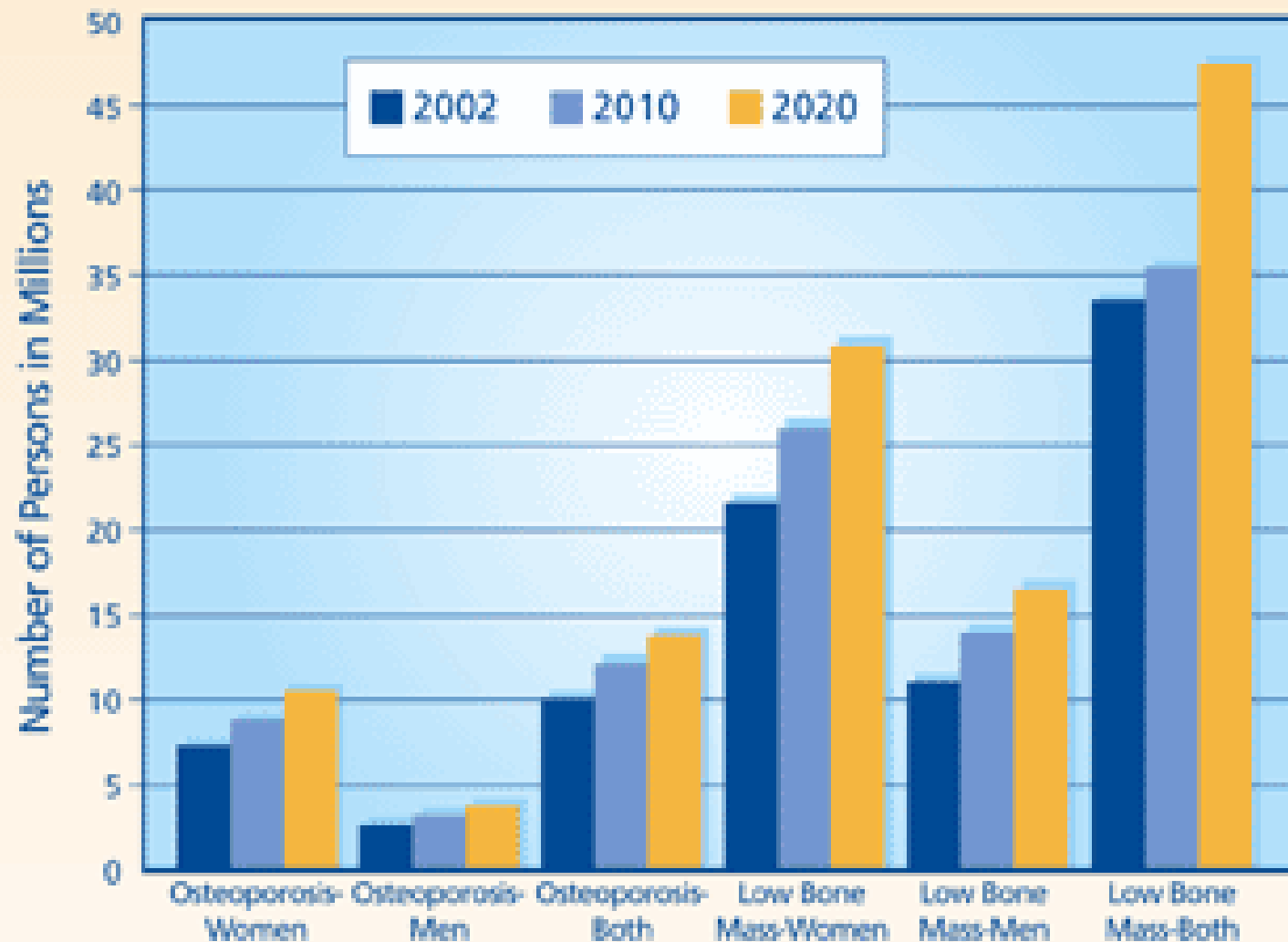
Age	Women	Men
Puberty to mid-20s & 30s	Bone mass increases rapidly, reaching peak bone mass	
Mid-30s to 40s	A few years of stability, then slow bone loss	No risk factors bone loss 1% / yr
Mid-40s to 50s	Menopause, then rapid bone loss $\geq 7\%$ / yr for ≥ 7 yrs	With risk factors bone loss $\geq 6\%$ / yr
Mid-50s to late life	Risk factors: low calcium intake, smoking, alcoholism, certain medications of 1% to 2% / yr	

Both men and women lose predominantly cancellous (vertebral) bone.

EPIDEMIOLOGY OF OSTEOPOROTIC FRACTURES

- **High prevalence**
 - 1.25 million female & 500,000 male hip fractures worldwide (1990)
 - 250,000 hip & 500,000 vertebral fractures in U.S. annually
- **Serious consequences**
 - ↓ quality of life, function, independence
 - ↑ morbidity & mortality (50% of women do not recover prior function after hip fracture; 20% excess mortality in year after hip fracture)
- **Costs**
 - > \$14 billion in U.S.

Estimates of Prevalence of Low Bone Mass and Osteoporosis from National Osteoporosis Foundation 2002 figures



Source: Wehren L (2002)

DEFINITIONS

- **Osteopenia**
 - **Bone mineral density (BMD) measurement at any site > 1 but ≤ 2.5 standard deviations below the young adult standard**
 - **T score < -1 but ≥ -2.5**

Definitions

- **Osteoporosis**
 - BMD measurement at any site > 2.5 standard deviations below the young adult standard with or without previous fracture
 - T score of < -2.5

PATHOGENESIS OF OSTEOPOROSIS

- Estrogen deficiency
- Calcium deficiency & secondary hyperparathyroidism
- Androgen deficiency
- Changes in bone formation
- Secondary causes and medications

ESTROGEN DEFICIENCY

Factors that play a role in bone loss of estrogen deficiency include:

- **Interleukin-1**
- **Interleukin-1 receptor antagonist**
- **Interleukin-6**
- **Tumor necrosis factor**

CALCIUM DEFICIENCY AND SECONDARY HYPERPARATHYROIDISM

- Aging skin & ↓ sunlight exposure ↓ conversion vitamin D₂ by ultraviolet light → vitamin-D deficiency
- Vitamin-D insufficiency → ↓ absorption of calcium
- Older adults tend to ingest inadequate amounts of calcium and vitamin D
- PTH ↑ in order to maintain serum levels of calcium
- When chronically elevated, PTH is a potent stimulator of bone resorption

ANDROGEN DEFICIENCY

- **Men with estrogen deficiency or resistance have ↓ bone mass and failure of epiphyseal closure**
- **Severe male hypogonadism can cause osteoporosis**
- **The effect of moderate decreases in testosterone levels in aging men on rate of bone loss is uncertain**

CHANGES IN BONE FORMATION

With aging and menopause:

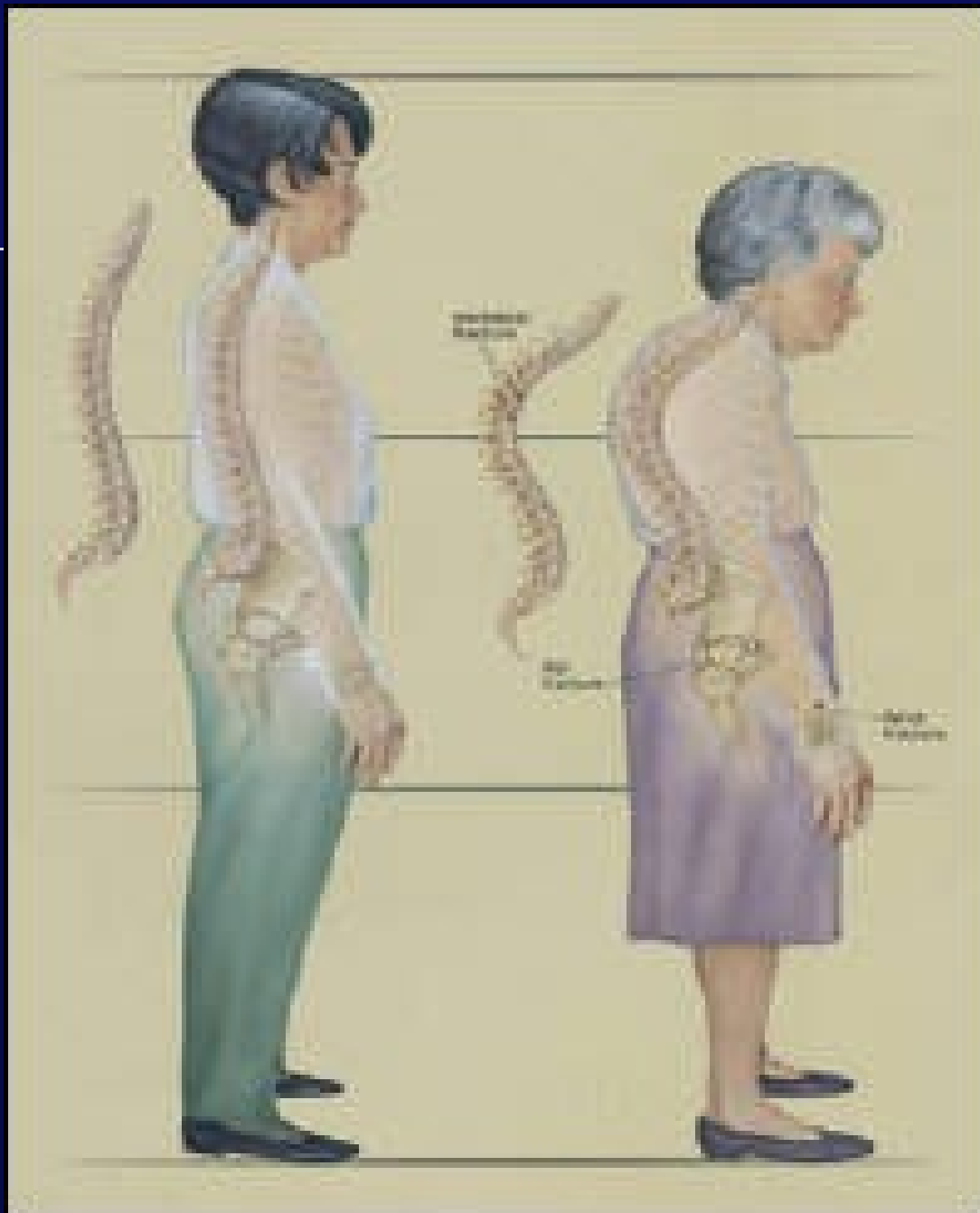
- **Osteoblast activity decreases**
- **Bone resorption increases**
- **Growth factors (e.g., transforming growth factor B and insulin-like growth factor 1) may be impaired, resulting in decreased osteoblast function**

SECONDARY CAUSES OF BONE LOSS

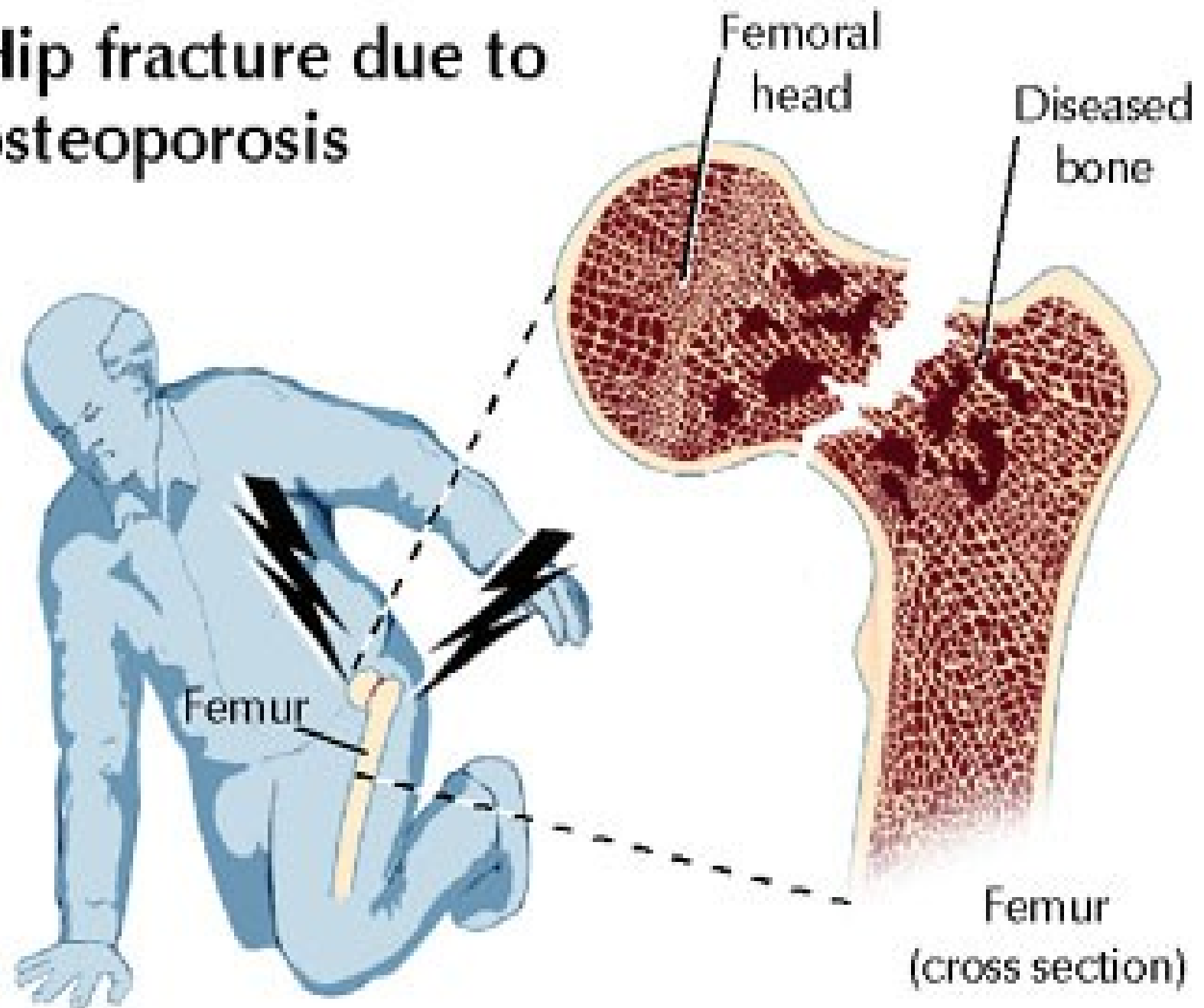
- Cushing's Disease
- Primary hyperparathyroidism
- Hyperthyroidism
- Hypogonadism
- Multiple myeloma
- Osteomalacia
- Paget's Disease
- Primary hyperparathyroidism
- Malabsorption syndromes (gastrectomy)

SECONDARY CAUSES OF BONE LOSS: MEDICATIONS

- **Glucocorticoids**
- **Excess thyroid supplement**
- **Anticonvulsants**
- **Methotrexate**
- **Cyclosporine**
- **Heparin**



Hip fracture due to osteoporosis



EVALUATION

- Measure bone density
- Assess for secondary causes of bone loss
- Use of biochemical markers in clinical practice is controversial

BMD MEASUREMENT

- Best predictor of fracture
 - **Relative risk of fracture is 10 × greater in women in the lowest quartile than in those in highest quartile**

DEXA

- **Dual-energy radiographic absorptiometry (DEXA)**
 - Preferred method of measurement
 - Can measure hip, anterior-posterior spine, lateral spine, and wrist
 - Cost = \$200 to \$300
 - Covered by Medicare and Medicaid if indications for use are met



INDICATIONS FOR BMD TESTING

- Postmenopausal women with multiple risk factors
- Postmenopausal women with fractures
- Men with conditions indicating high risk
- Women and men with osteoporosis who have been on treatment for long time
- All women ≥ 65 years old at least once (recommended by USPSTF)

Indications For Bone Density Testing

- All women age 65 and older
- All men age 70 and older
- Adults with a fragility fracture
- Adults with a disease or condition associated with low bone density
- Adults taking medication associated with low bone density
- Anyone being treated for low bone density to monitor treatment effect
- Anyone not receiving therapy, in whom evidence of bone loss would lead to treatment

Women discontinuing treatment should be considered for bone density testing according to the indications listed above.

Which Skeletal Sites Should Be Measured?

Every Patient

- Spine
 - L1-L4
- Hip
 - Total Proximal Femur
- **Osteoporosis**
 - Femoral Neck
 - Trochanter

Some Patients

- Forearm (33% Radius)
 - If hip or spine cannot be measured
 - Hyperparathyroidism
 - Very obese

Use lowest T-score of these sites

Why -2.5?

“Such a cutoff value identifies approximately 30% of postmenopausal women as having osteoporosis using measurements made at the spine, hip or forearm. This is approximately equivalent to the lifetime risk of fracture at these sites.”

Diagnostic Classification

Classification	T-score
Normal	-1 or greater
Osteopenia	Between -1 and -2.5
Osteoporosis	-2.5 or less
Severe Osteoporosis	-2.5 or less and fragility fracture

Diagnosis Caveats

- T-score -2.5 or less does not always mean osteoporosis
 - Example: osteomalacia
- Clinical diagnosis of osteoporosis may be made with T-score greater than -2.5
 - Example: atraumatic vertebral fracture with T-score equals -1.9
- Low T-score does not identify the cause
 - Medical evaluation should be considered
 - Example: celiac disease with malabsorption

Treatment Guidelines

Summary of recommendations for pharmacologic therapy according to T-score from the National Osteoporosis Foundation (NOF) and the American Association of Clinical Endocrinologists (AACE)

Patient Profile	T-score	
	NOF	AACE
No Risk Factors	Less than -2.0	-2.5 or less
Risk Factors [†]	Less than -1.5	-1.5 or less

† Fragility fracture, family history of fracture, cigarette smoking, low body weight (<127 lbs.), etc.

RISK FACTORS FOR POSTMENOPAUSAL WOMEN

- Early menopause
- White or Asian race
- Sedentary life style
- Smoking
- Small frame
- Alcohol abuse
- Primary hyperparathyroidism
- Hyperthyroidism
- Glucocorticoid use

SCREENING FOR SECONDARY CAUSES

Disease	Recommended Laboratory Tests (bolded items are recommended routinely)
Cushing's disease	Electrolytes, 24-hour urinary cortisol
Hyperthyroidism	TSH, T ₄
Hypogonadism	Bioavailable testosterone
Multiple myeloma	CBC, serum electrophoresis, urine electrophoresis
Osteomalacia	Alkaline phosphatase, 25(OH)D
Paget's disease	Alkaline phosphatase
Primary hyperparathyroidism	Calcium, PTH

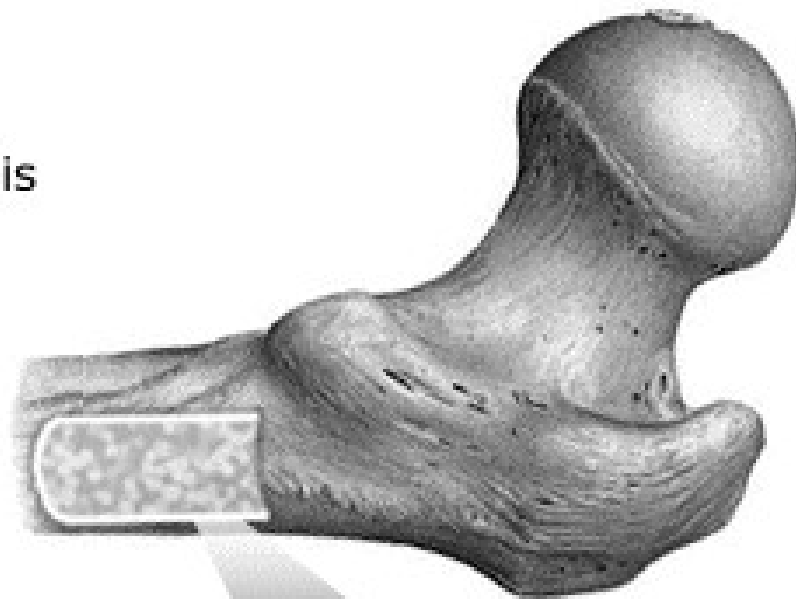
BIOCHEMICAL MARKERS OF BONE TURNOVER

- **May provide an early assessment of treatment efficacy**
- **Bone resorption markers**
 - Deoxypyridinoline cross-links
 - Cross-linked N-telopeptides of type I collagen
- **Bone formation marker**
 - Bone alkaline phosphatase

LIMITATIONS ON THE USE OF BIOCHEMICAL MARKERS

- Clinical use is controversial because of substantial overlap of values in women with high and low bone density or rate of bone loss
- Few studies have compared the response of a particular marker and bone density with goals of therapy

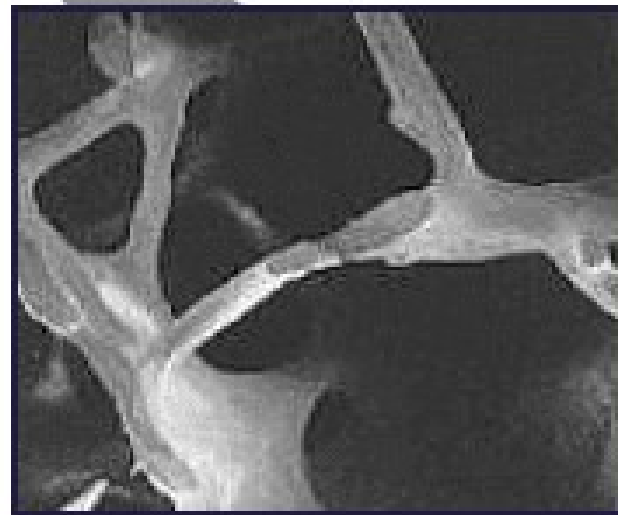
Section of bone
showing osteoporosis



Normal Bone



Osteoporotic Bone

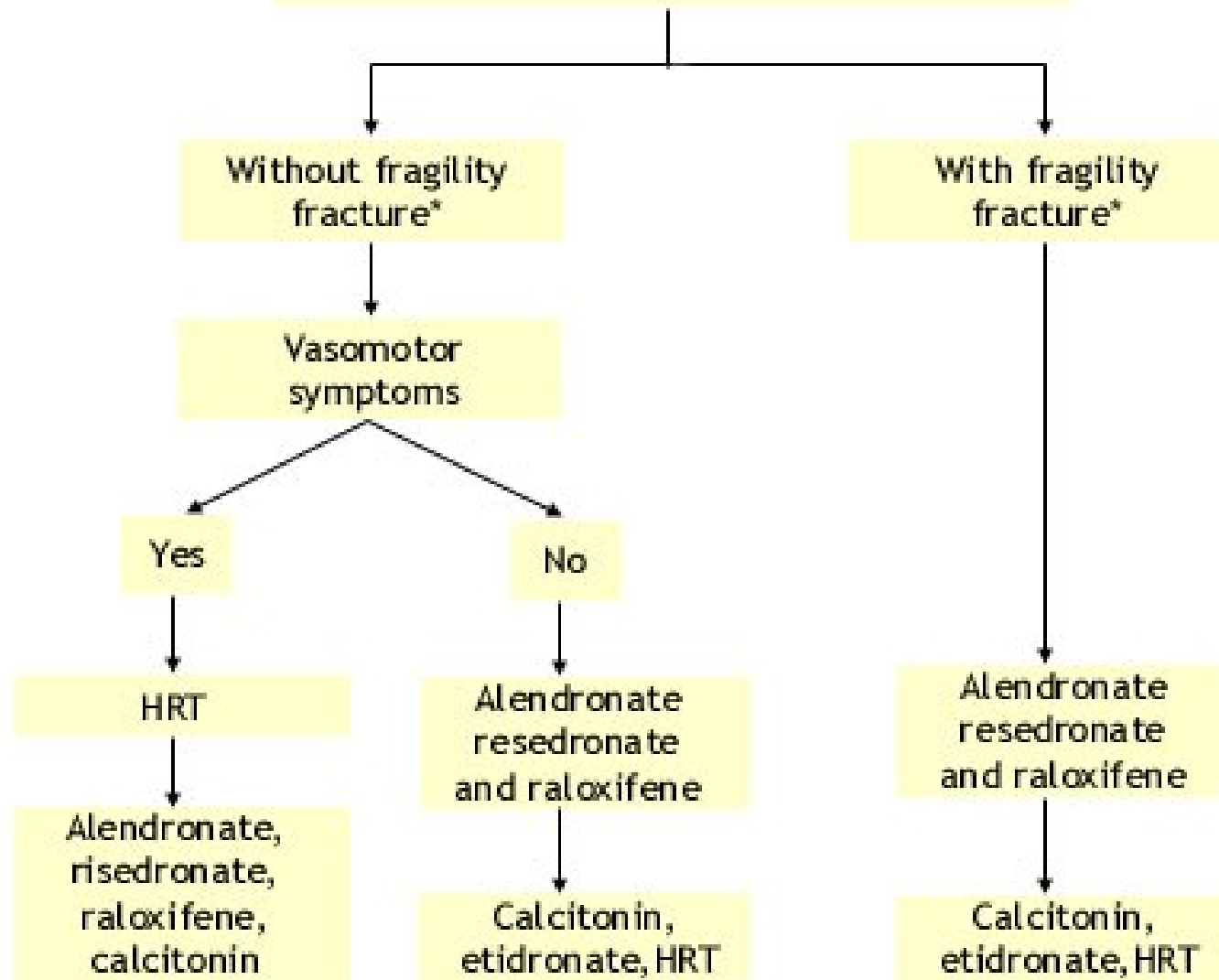


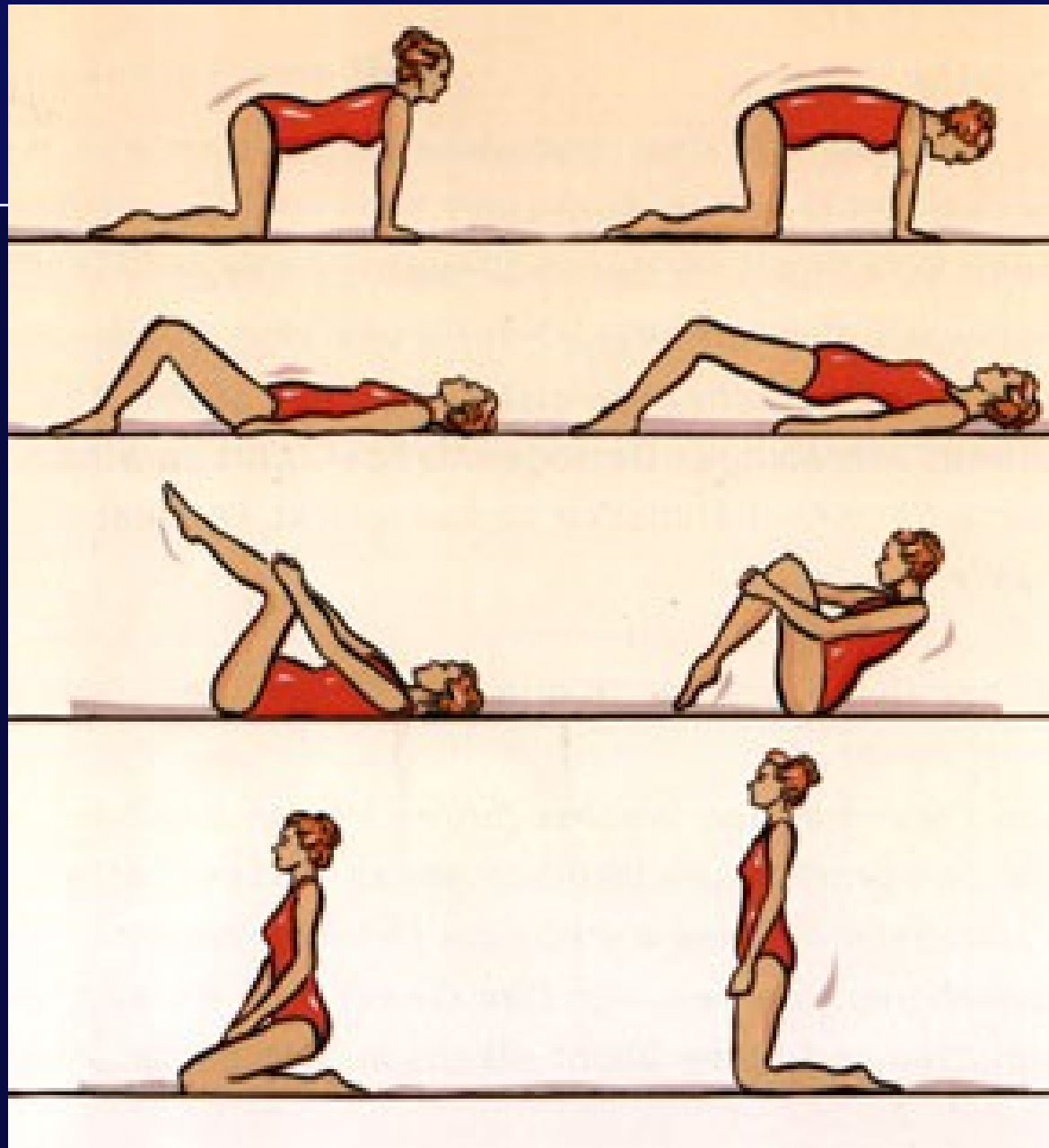
Reproduced from *J Bone Miner Res* 1995;10:21 with
permission of the American Society for Bone and Mineral Research

PREVENTING AND TREATING OSTEOPOROSIS

- Weight-bearing exercise
- Calcium and vitamin D
- Estrogen replacement
- Bisphosphonates
- Selective estrogen receptor modulators
- Calcitonin
- Investigational agents

Non-pharmacological treatment
Calcium: 1500 mg/day
Vitamin D: 800 IU/day
Physical activity: ≥ 30 min at least
3 times a week





THE ATHLETIC WOMAN'S SURVIVAL GUIDE

WITH ILLUSTRATIONS BY



The Athletic Woman's Survival Guide



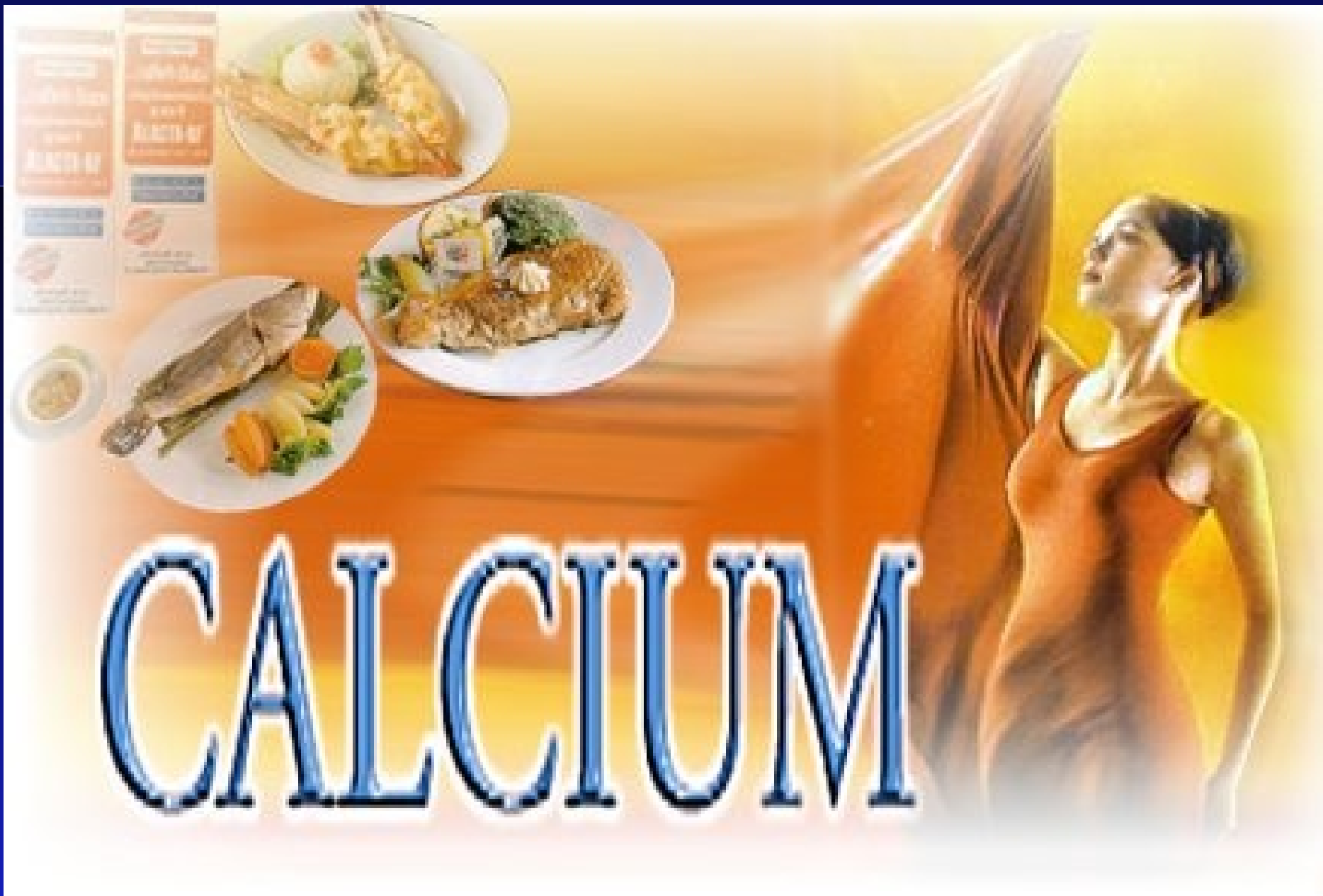
How to win the battle against

- eating disorders
- amenorrhea
- osteoporosis

Carol L. Otis, MD
Roger Goldingay

EXERCISE

- Marked decrease in physical activity or immobilization → decline in bone mass
- Walking, a weight-bearing exercise, can be recommended for all adults
- Start slowly and gradually increase the number of days and time spent walking each day



CALCIUM & VITAMIN D

- Calcium and vitamin D maintain or increase bone density in postmenopausal women & help prevent hip and nonvertebral fractures in all older adults
- 1200 mg / day of calcium: men 65 years and older & postmenopausal women
- 400-800 IU / day of vitamin D: regardless of sunlight exposure to offset skin changes that ↓ efficient use of UV light to synthesize vitamin D precursors

ESTROGEN REPLACEMENT

Reasons to use ERT to prevent or treat osteoporosis include:

- Use results in 30% to 70% reduction in hip-fracture incidence
- Prevents bone loss at hip & spine when initiated within 10 years of menopause
- Postmenopausal Estrogen-Progestin Intervention (PEPI) trial: older women, women with low initial BMD, & women with no previous HRT gained more bone than others

ESTROGEN REPLACEMENT: LIMITATIONS

- **Side effects**
- **Concerns about increased risks of endometrial and breast cancer**
- **Unclear effect on risk of cardiovascular disease**

BISPHOSPHONATES: ALENDRONATE

- **Rationale**

- **Approved for osteoporosis prevention & treatment**
- **In comparison with placebo:**
 - ↑ bone density of spine & hip
 - ↓ vertebral fracture rate

- **Dosing**

- **Prevention: 5 mg / day; treatment: 10 mg / day**
- **Once-weekly dosing (70 mg) as effective as daily dosing**
- **Consider combining with estrogen if monotherapy not effective**

- **Side effects**

- **GI: abdominal pain, dyspepsia, esophagitis, nausea, vomiting, diarrhea**
- **Musculoskeletal pain**

OTHER BISPHOSPHONATES

- **Residronate (Actonel)**
 - **Approved for osteoporosis prevention & treatment of osteoporosis: 5 mg / day**
 - **In comparison with placebo:**
 - ↑ bone density of spine & hip
 - ↓ new vertebral fracture rate
 - **GI side effects**
- **Etidronate (Didronel)**
 - **Not approved for treatment of osteoporosis**
 - **Use for idiopathic osteoporosis only if other treatments are ineffective**

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs)

- **Act as estrogen agonists in bone and heart**
- **Act as estrogen antagonists in breast and uterine tissue**
- **Potential for preventing osteoporosis without the increased risk of breast or uterine cancer**

SERMs: RALOXIFENE

- **Rationale**
 - **Approved for osteoporosis prevention & treatment in postmenopausal women**
 - **In comparison with placebo:**
 - ↓ vertebral fractures by 60%
 - ↓ breast cancer (relative risk 0.24)
 - ↓ bone turnover & maintained hip & total body bone density
 - **↓ total cholesterol and LDL levels**
- **Side effects**
 - **Flu-like symptoms, hot flushes, leg cramps**
 - **Peripheral edema**

CALCITONIN

- **Rationale**

- **Hormonal inhibitor of bone resorption**
- **In comparison with placebo:**
 - ↓ vertebral fractures and ↑ spine bone density
 - No statistical ↓ in hip fractures
- **May be less effective than other antiresorptives**
- **Possible analgesic effect in women with painful vertebral compression fractures**

- **Dosing**

- **Subcutaneous injection**
- **Nasal spray (fewer reported side effects, greater patient acceptance, may be less effective)**

INVESTIGATIONAL AGENTS (1 of 2)

- **Bisphosphonates**
 - pamidronate, ibandronate, tiludronate
- **SERMs**
- **Parathyroid hormone (PTH)**
 - Although leads to \uparrow bone resorption when continuously elevated
 - Can \uparrow bone mass, trabecular connectivity, mechanical strength when given intermittently

INVESTIGATIONAL AGENTS (2 of 2)

- **Fluoride**

- ↑ spine bone density, but increase not consistently associated with ↓ in vertebral fractures
- May ↑ rate of appendicular fractures

- **Statins (observational studies)**

- 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors
- May be associated with ↓ fracture rate

Patient Education

- **Educate**
- **Improve adherence to medications**
- **Establish baseline BMD measurement**
- **Follow up: measure BMD every 1-2 years**

MODIFYING RISK FACTORS

- Encourage regular, weight-bearing exercise
- Encourage adequate calcium and vitamin D intake
- Encourage lower animal protein intake
- Encourage smoking cessation
- Use medications that may ↑ osteoporosis risk with caution (e.g., anticonvulsants, cyclosporine, glucocorticoids, long-term heparin, methotrexate, thyroid hormone replacement)

Spinal osteoporosis

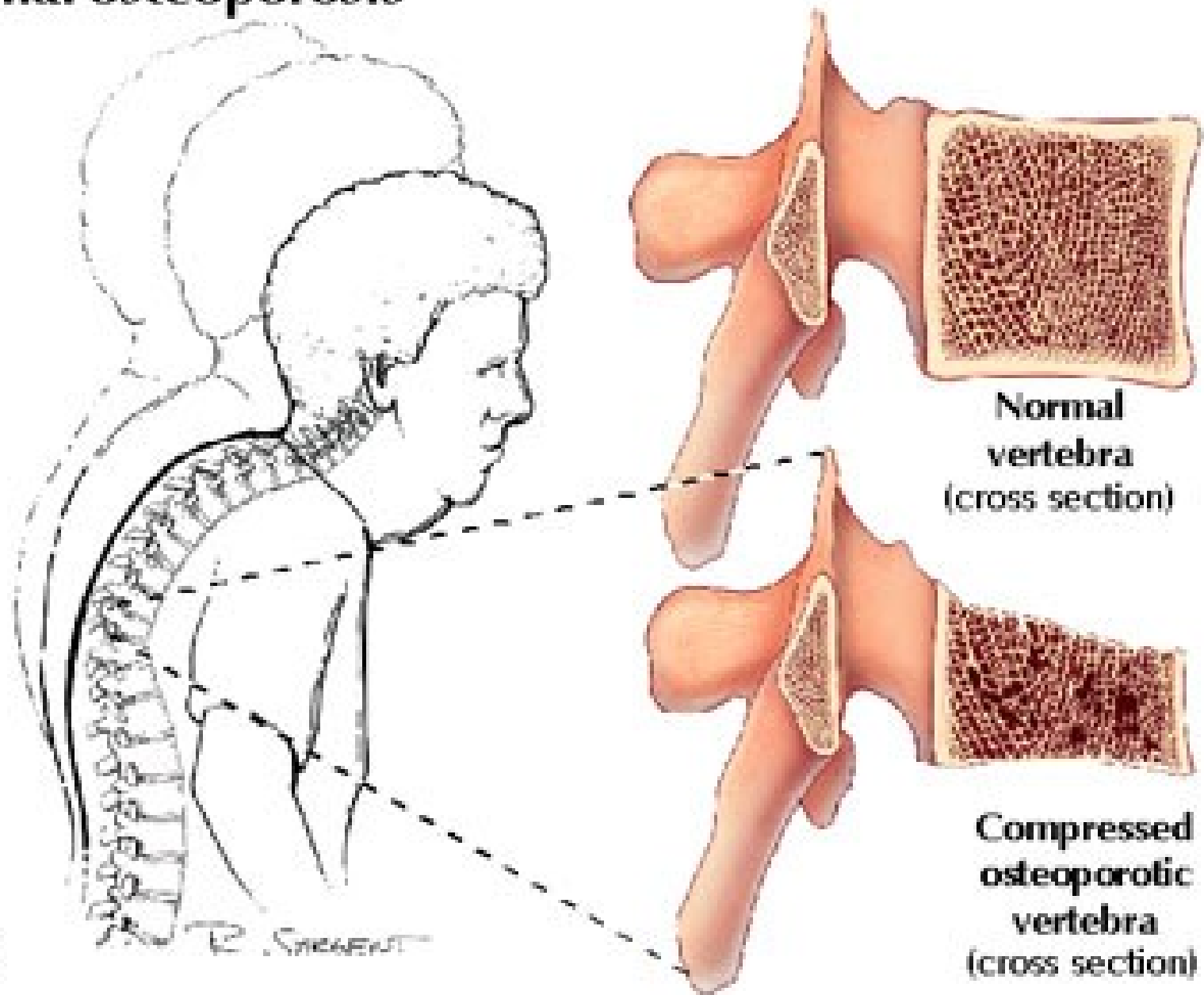


Fig. 1

VERTEBRAL FRACTURES

- **Asymptomatic (the majority)**
 - Diagnosed by spinal radiographs
 - ↑ kyphosis or ↓ height
 - Chronic back pain due to spinal changes that occur with vertebral compression
- **Symptomatic**
 - Pain usually lasts 2 to 4 weeks
 - Can be debilitating

MANAGING VERTEBRAL FRACTURES

- **Medications**
 - NSAIDs and calcitonin
 - Narcotics commonly required for pain control
- **Physical therapy**
 - Important for both acute and chronic pain
 - Postural exercises
 - Alternative modalities for ↓ pain
- **Education, support groups**

OSTEOMALACIA

- **Impairment of bone mineralization**
- **Clinical syndrome: pain, myopathy, fracture**
- **Etiology**
 - Vitamin-D deficiency from inadequate intake
 - Excessive use of phosphate-binding antacids
 - Chronic use of anticonvulsants
 - Chronic renal failure
 - Hepatobiliary disease
 - Malabsorption

DIAGNOSING OSTEOMALACIA

- **Symptoms and Signs**
 - Diffuse bone pain, proximal weakness, myopathy, fracture
 - Waddling gait resulting from hip pain, thigh weakness
- **Definitive Diagnosis**
 - Bone biopsy
- **Laboratory studies**
 - Elevated alkaline phosphatase
 - Low phosphate, 25(OH)D levels
 - Low or normal calcium
- **Radiography**
 - Osteopenia or pseudofractures

TREATING OSTEOMALACIA

- **Goal: manage the underlying cause**
- **Replete vitamin-D deficiency:**
 - 1000 IU / day
- **Correct hypophosphatemia:**
 - neutral phosphate salts 500 mg qid
- **Supplement patients on long-term anticonvulsants:**
 - vitamin D 400-800 IU / day
- **If due to hepatobiliary disease, treat with 25(OH)D**
- **If due to renal failure, treat with 1,25(OH)₂D**

SUMMARY (1 of 2)

- **Osteoporosis is prevalent among older adults and is associated with high personal and financial costs as well as mortality**
- **Osteopenia and osteoporosis can be diagnosed with BMD using dual-energy radiographic absorptiometry**
- **Evaluation of patients with osteoporosis should include assessment for secondary causes of bone loss**

SUMMARY (2 of 2)

- **Osteoporosis prevention and treatment combines risk reduction, exercise, calcium and vitamin-D supplementation, hormones, and other pharmacotherapies**
- **Pain of osteoporotic vertebral fractures can be treated with NSAIDs, calcitonin, and narcotics, as well as physical therapy**
- **Osteomalacia may cause pain, myopathy, and fracture; the underlying cause should be treated**

CASE #1 (1 of 3)

- **A 68-year-old white woman, whose mother and maternal aunt had late-life hip fractures, asks you about osteoporosis prevention. She is healthy and walks 4 or 5 days each week. Her only medications are calcium and vitamin D supplements.**
- **At a health fair, she had an ultrasonography of the heel, with a T score of -1.5. She is reluctant to take additional drugs.**

CASE #1 (2 of 2)

- Which of the following is most appropriate for this patient?
 - Reassurance and continuation of the current regimen
 - Quantitative computed tomography (QCT) of the spine
 - **Dual-energy x-ray absorptiometry (DEXA scan) of the spine and hip**
 - Alendronate

CASE #2 (1 of 3)

- **A 75-year-old white man has back pain after gardening and is found to have a T10 vertebral compression fracture. The patient has no other symptoms and has always been in good health except for mild hypertension that is treated with a diuretic.**
- **He is very active and does weight-bearing exercise for 1-2 hours each day. He does not smoke cigarettes and drinks alcohol only occasionally.**

CASE #2 (2 of 3)

- Which of the following is the most likely cause of the fracture?
 - **Idiopathic osteoporosis**
 - **Testosterone deficiency**
 - **Longstanding corticosteroid use**
 - **Chronic malabsorption**
 - **Metastatic carcinoma**